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CLINICAL THERAPEUTICS

Single Intravenous Dose of Oritavancin for Treatment of Acute Skin and Skin Structure Infections Caused by Gram-Positive Bacteria: Summary of Safety Analysis from the Phase 3 SOLO Studies

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ABSTRACT Oritavancin is a lipoglycopeptide with bactericidal activity against Gram-positive organisms. Its rapid concentration-dependent bactericidal activity and long elimination half-life allow single-dose treatment of acute bacterial skin and skin structure infections (ABSSSI). SOLO I and SOLO II were randomized, double-blind studies evaluating the efficacy and safety of a single 1,200-mg intravenous (i.v.) dose of oritavancin versus twice-daily i.v. vancomycin for 7 to 10 days in ABSSSI patients. Safety data from both studies were pooled for safety analysis. The database comprised pooled safety data for 976 oritavancin-treated patients and 983 vancomycin-treated patients. The incidences of adverse events, serious adverse events, and discontinuations due to adverse events were similar for oritavancin (55.3, 5.8, and 3.7%, respectively) and vancomycin (56.9, 5.9, and 4.2%, respectively). The median time to onset (3.8 days versus 3.1 days, respectively) and the duration (3.0 days for both groups) of adverse events were also similar between the two groups. The most frequently reported events were nausea, headache, and vomiting. Greater than 90% of all events were mild or moderate in severity. There were slightly more infections and infestations, abscesses or cellulitis, and hepatic and cardiac adverse events in the oritavancin group; however, more than 80% of these events were mild or moderate. Subgroup analyses did not identify clinically meaningful differences in the incidence of adverse events attributed to oritavancin. A single 1,200-mg dose of oritavancin was well tolerated and had a safety profile similar to that of twice-daily vancomycin. The long elimination half-life of oritavancin compared to that of vancomycin did not result in a clinically meaningful delay to the onset or prolongation of adverse events. (This study has been registered at ClinicalTrials.gov under registration no. NCT01252719 and NCT01252732.)

KEYWORDS single-dose treatment, clinical safety, 60-day safety follow-up, elimination half-life, single dose

Acute bacterial skin and skin structure infections (ABSSSI) are among the most common infections seen in clinical practice (1, 2). These infections may require systemic antibiotic therapy, surgical management, and hospitalization and, if untreated, may become severe or life-threatening (3, 4). The economic burden of ABSSSI remains substantial (2) and is driven by high costs of hospitalization (5, 6) and the need for intravenous (i.v.) treatment with agents that require once- or twice-daily dosing for at least 7 to 10 days (7–9).

Empirical ABSSSI treatment often requires agents that are active against methicillin-

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resistant *Staphylococcus aureus* (MRSA), which continues to be the predominant causative pathogen in the United States and many other countries (10, 11). In the United States, community-associated MRSA rates of 40 to 60% are common (12–14), and as a result, vancomycin is often prescribed to treat ABSSSI. However, vancomycin is associated with a range of adverse events (AEs), including nephrotoxicity, hypersensitivity, ototoxicity, neutropenia, and injection site reactions, including phlebitis (15, 16).

Managing certain skin and skin structure infections with outpatient parenteral antibiotic therapy (OPAT) can facilitate earlier discharge but may not overcome the limitations of multiple administrations, incomplete medication adherence, and the complexity of serum drug monitoring (17). Likewise, even oral therapy for outpatient treatment of skin and skin structure infections may be associated with suboptimal adherence (18) and correspondingly poor clinical outcomes (19).

Oritavancin, a semisynthetic lipoglycopeptide antibiotic, has three mechanisms of action (20–22) that provide concentration-dependent bactericidal activity (23). Oritavancin exhibits potent activity against Gram-positive pathogens, including MRSA (24–26), and has an extended plasma elimination half-life of 245 h (27). No therapeutic drug monitoring is necessary, and no dose adjustment is required for patients with mild to moderate renal function impairment, with mild to moderate hepatic impairment, or on the basis of age, gender, race, weight, or diabetes status (27).

Two phase 3 studies in adults with ABSSSI, SOLO I and SOLO II (28, 29), demonstrated the safety and efficacy of a single 1,200-mg dose of oritavancin compared to twice-daily vancomycin for 7 to 10 days. Since the completion of the SOLO studies, real-world evidence shows that for outpatient management of ABSSSI, oritavancin offers comparable effectiveness, greater economy, and reduced use of health care resources in comparison with the standard-of-care therapy (30).

Efficacy outcomes using pooled data from SOLO I and SOLO II have recently been presented (31); the safety outcomes determined using pooled data are presented here. Events related to potential glycopeptide effects (hypersensitivity, infusion-related reactions), general antibiotic-related effects (*Clostridium difficile*-associated diarrhea [CDAD]), organ systems (i.e., renal, hepatic, and cardiac systems), and other key safety topics (e.g., infections/infestations) were also assessed. A prior abstract presented a partial assessment of oritavancin safety in certain patient subgroups within the pooled SOLO studies (32).

RESULTS

Patient disposition, demographics, and baseline characteristics. The demographic and baseline disease characteristics of the patients in the oritavancin and vancomycin groups were comparable (Table 1). There were 1,959 subjects in the safety population. Of these, 976 received oritavancin (473 in SOLO I, 503 in SOLO II) and 983 subjects received vancomycin (481 in SOLO I study, 502 in SOLO II). Most patients were male, white, and $<$65 years of age. The median weight was approximately 75 kg in both groups, and the median body mass index (BMI) was approximately 26 kg/m^2; similar proportions of patients in each group (approximately 28%) were obese (BMI $>$ 30 kg/m^2). A slightly higher proportion of patients in the oritavancin group (oritavancin, 7.2%; vancomycin, 5.5%) had moderate renal impairment (creatinine clearance [CL_{CR}], 30 to $<$60 ml/min). There were no clinically relevant differences in either the medical history or other baseline comorbidities between the oritavancin and vancomycin groups (not shown). In total, 89.5 and 86.4% of the patients in the oritavancin and vancomycin groups, respectively, completed the study drug course of therapy (see Table S1 in the supplemental material). The median duration of treatment was 8 days in both the oritavancin/placebo and vancomycin groups.

Discontinuations from study drug were balanced between the treatment groups, with the primary reasons being AEs (oritavancin group, 3.4%; vancomycin group, 3.3%) and the patient withdrew consent (oritavancin group, 2.7%; vancomycin group, 4.7%). A total of 90.8 and 88.6% of patients in the oritavancin and vancomycin groups, respectively, completed the study. The most common reasons for not completing the

TABLE 1 Patient demographics and baseline characteristics (safety population)[a]

Characteristic	Value(s) for patients receiving: Oritavancin (n = 976)	Vancomycin (n = 983)
Age (yr)		
Mean (SD)	45.6 (13.8)	44.3 (14.4)
Median (min, max)	46.0 (18, 89)	45.0 (18, 93)
No. (%) of patients ≥65 yr of age	86 (8.8)	77 (7.8)
No. (%) of male patients	638 (65.4)	645 (65.6)
Wt (kg)		
Mean (SD)	78.9 (22.7)	80.3 (25.0)
Median (min, max)	75.0 (35, 200)	75.6 (36, 220)
No. (%) of patients with wt (kg) of:		
<60	174 (17.8)	165 (16.8)
60 to <100	651 (66.7)	656 (66.7)
≥100	151 (15.5)	162 (16.5)
BMI (kg/m²)		
Mean (SD)	27.7 (7.61)	27.8 (7.95)
Median (min, max)	26.2 (15, 74)	25.9 (14, 84)
No. (%) of patients with BMI of:		
<25	405 (41.5)	421 (42.8)
25 to <30	294 (30.1)	282 (28.7)
≥30	277 (28.4)	280 (28.5)
No. (%) of patients with hepatic impairment[b]		
Yes	29 (3.0)	27 (2.7)
No	947 (97.0)	956 (97.3)
No. (%) of patients with CL_{CR} (ml/min) of:		
<30	7 (0.7)	7 (0.7)
30 to <60	70 (7.2)	54 (5.5)
60 to <90	190 (19.5)	183 (18.6)
≥90	688 (70.5)	716 (72.8)
No. (%) of patients with the following lesion type:		
Wound infection	283 (29.0)	281 (28.6)
Cellulitis/erysipelas	385 (39.4)	402 (40.9)
Major cutaneous abscess	308 (31.6)	300 (30.5)
Median lesion size at baseline (cm²)	267	274
No. (%) of patients with diabetes	138 (14.1)	141 (14.3)
No. (%) of patients who met SIRS criteria at baseline[c]	169 (17.3)	173 (17.6)
No. (%) of patients with fever (temp, ≥38°C)	186 (19.0)	185 (18.9)
No. (%) of patients with confirmed MRSA infection	204 (20.9)	201 (20.5)

[a]min, minimum; max, maximum; BMI, body mass index; CL_{CR}, creatinine clearance; SIRS, systemic inflammatory response syndrome; MRSA, methicillin-resistant *Staphylococcus aureus*.
[b]Hepatic impairment was defined by baseline alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels >3 times the upper limit of the normal range (ULN) or a total bilirubin concentration >2 times the ULN.
[c]Systemic inflammatory response syndrome criteria were defined as two of the following: a temperature of >38°C, a pulse of >90 beats per minute (bpm), a respiratory rate of >20 breaths per minute, a white blood cell (WBC) count of >12,000 mm³ or <4,000 mm³, or >10% bandemia.

study were loss to follow-up (oritavancin group, 5.1%; vancomycin group, 7.0%) and withdrawal of consent (oritavancin group, 3.1%; vancomycin group, 3.6%).

Overall summary of adverse events. The overall frequency of treatment-emergent adverse events (TEAEs; oritavancin group, 55.3%; vancomycin group, 56.9%) was similar between the two groups (Table 2). Greater than 90% of TEAEs were mild or moderate in severity in both groups, and the distribution of mild, moderate, and severe TEAEs was similar. Fewer TEAEs were judged by the investigator to be related to oritavancin (22.2%) than to vancomycin (28.4%). The frequency of AEs leading to study drug

TABLE 2 Overall summary of AEs (safety population)[a]

AE	No. (%) of patients receiving:	
	Oritavancin (n = 976)	Vancomycin (n = 983)
TEAE	540 (55.3)	559 (56.9)
Mild	324 (33.2)	331 (33.7)
Moderate	165 (16.9)	180 (18.3)
Severe	51 (5.2)	48 (4.9)
Study drug related	217 (22.2)	279 (28.4)
Leading to study drug discontinuation	36 (3.7)	41 (4.2)
SAE	57 (5.8)	58 (5.9)
Study drug related	5 (0.5)	4 (0.4)
Leading to study drug discontinuation	21 (2.2)	19 (1.9)
Death	2 (0.2)	3 (0.3)

[a]Each adverse event was reported using its maximum severity. AE, adverse event; TEAE, treatment-emergent adverse event; SAE, serious adverse event.

discontinuation was comparable in the oritavancin (3.7%) and vancomycin (4.2%) groups. The most frequently reported AEs were nausea, headache, vomiting, and cellulitis in the oritavancin group and nausea, pruritus, headache, and vomiting in the vancomycin group (Table 3). The most frequently reported AEs leading to study drug discontinuation were cellulitis and osteomyelitis in the oritavancin group and cellulitis, hypersensitivity, pruritus, and skin infection in the vancomycin group (Table 4).

TABLE 3 AEs in ≥2% patients and SAEs in ≥2 patients in either treatment group, regardless of relatedness to study drug (safety population)[a]

Patient group and preferred term	No. (%) of patients receiving:	
	Oritavancin (n = 976)	Vancomycin (n = 983)
Patients with ≥1 AE	540 (55.3)	559 (56.9)
Nausea	97 (9.9)	103 (10.5)
Headache	69 (7.1)	66 (6.7)
Vomiting	45 (4.6)	46 (4.7)
Cellulitis	37 (3.8)	32 (3.3)
Diarrhea	36 (3.7)	32 (3.3)
Constipation	33 (3.4)	38 (3.9)
Infusion site extravasation	33 (3.4)	33 (3.4)
Pyrexia	30 (3.1)	31 (3.2)
Pruritus	29 (3.0)	73 (7.4)
Abscess limb	27 (2.8)	13 (1.3)
ALT level increased	27 (2.8)	15 (1.5)
Dizziness	26 (2.7)	26 (2.6)
Infusion site phlebitis	24 (2.5)	15 (1.5)
Tachycardia	24 (2.5)	11 (1.1)
Insomnia	21 (2.2)	25 (2.5)
Patients with ≥1 SAE	57 (5.8)	58 (5.9)
Cellulitis	11 (1.1)	12 (1.2)
Osteomyelitis	4 (0.4)	1 (0.1)
Abscess limb	3 (0.3)	0
Pneumonia	3 (0.3)	0
Skin infection	3 (0.3)	3 (0.3)
Subcutaneous abscess	3 (0.3)	1 (0.1)
Diabetic ketoacidosis	2 (0.2)	1 (0.1)
Hypoxia	2 (0.2)	1 (0.1)
Tenosynovitis	2 (0.2)	0
Arthritis bacterial	1 (0.1)	2 (0.2)
Deep vein thrombosis	1 (0.1)	2 (0.2)
Dyspnea	1 (0.1)	2 (0.2)
Pyrexia	0	2 (0.2)
Respiratory failure	0	2 (0.2)

[a]AE, adverse event; SAE, serious adverse event; ALT, alanine aminotransferase.

TABLE 4 AEs leading to discontinuation of study drug in ≥2 patients in either treatment group (safety population)[a]

	No. (%) of patients receiving:	
Preferred term	Oritavancin (n = 976)	Vancomycin (n = 983)
Any AE	36 (3.7)	41 (4.2)
Cellulitis	4 (0.4)	5 (0.5)
Osteomyelitis	3 (0.3)	1 (0.1)
Abscess limb	2 (0.2)	0
Infection	2 (0.2)	0
Infusion site phlebitis	2 (0.2)	0
Pruritus	2 (0.2)	4 (0.4)
Subcutaneous abscess	2 (0.2)	1 (0.1)
Drug hypersensitivity	1 (0.1)	2 (0.2)
Rash macular	1 (0.1)	2 (0.2)
Skin infection	1 (0.1)	4 (0.4)
Drug exposure during pregnancy	0	2 (0.2)
Hypersensitivity	0	5 (0.5)
Pyrexia	0	2 (0.2)
Rash	0	2 (0.2)
Sepsis	0	2 (0.2)
Skin bacterial infection	0	2 (0.2)

[a]AE, adverse event.

Comparable numbers of patients in each group experienced a serious adverse event (SAE) (Table 2). The most frequent SAEs in the oritavancin group were cellulitis, which occurred in 11 (1.1%) oritavancin-treated patients and 12 (1.2%) vancomycin-treated patients, and osteomyelitis, which occurred in 4 (0.4%) oritavancin-treated patients and 1 (0.1%) vancomycin-treated patient (Table 3). No other SAE was reported in more than 3 patients in either group. The proportion of patients that experienced study drug-related SAEs was low and balanced between the groups (oritavancin group, 0.5%; vancomycin group, 0.4%) (Table 2). SAEs assessed by the investigator to be related to study drug were leukocytoclastic vasculitis, urticaria, mouth ulceration, drug hypersensitivity, and bronchospasm in the oritavancin group and thrombocytosis, hypersensitivity, drug hypersensitivity, and anaphylactoid reaction in the vancomycin group. Each study drug-related SAE was reported by 1 patient.

Deaths were infrequent for both treatment groups (Table 2), and all deaths were considered unrelated to study drug by the investigator. Two oritavancin-treated patients (0.2%) died; one died due to sepsis, and the other died due to electromechanical dissociation. Three vancomycin-treated patients (0.3%) died; one patient each died from septic shock, advanced dementia with Parkinsonism, and acute myocardial infarction.

Time to onset and duration of adverse events. The median time to the onset of AEs was 3.8 days in the oritavancin group (range, 0 to 62 days) and 3.1 days in the vancomycin group (range, 0 to 65 days) (Table 5). AEs had a median duration of 3.0 days in both groups. The majority of AEs occurred within the first 3 days of the study (64.8% in the oritavancin group, 66.2% in the vancomycin group). The median time to SAE onset was 10.6 days in the oritavancin group (range, 0 to 62 days) and 19.6 days in the vancomycin group (range, 0 to 56 days) (Table 5). SAEs had a median duration of 7.0 days in the oritavancin group and 4.0 days in the vancomycin group. The distributions of AE onset (Fig. 1A) and duration (Fig. 1B) were similar for the oritavancin and vancomycin groups.

Adverse events of interest for vancomycin and oritavancin. Vancomycin- and glycopeptide-related AEs of interest include hypersensitivity, infusion site reactions/phlebitis, vestibular toxicity/ototoxicity, and hematologic effects (33). The incidence of hypersensitivity reactions in the safety population was lower in the oritavancin group (7.7%) than in the vancomycin group (14.1%). The most frequent hypersensitivity reaction in both groups was pruritus, which occurred in 29 (3.0%) oritavancin-treated patients and 73 (7.4%) vancomycin-treated patients. The majority of these events were

TABLE 5 Distribution of onset and duration of AEs (safety population)[a]

Variable	Event	Statistic	Value(s) for patients receiving: Oritavancin (*n* = 976)	Vancomycin (*n* = 983)
Onset (days)	All TEAEs	No. of patients	1,535	1,530
		Mean (SD)	8.0 (11.92)	7.0 (11.26)
		Median	3.8	3.1
		IQR (Q3-Q1)	7.4	6.0
		Min, max	0, 62	0, 65
	All related TEAEs	No. of patients	417	583
		Mean (SD)	3.4 (4.88)	3.3 (5.15)
		Median	2.0	1.7
		IQR (Q3-Q1)	4.3	4.0
		Min, max	0, 46	0, 56
	All SAEs	No. of patients	73	79
		Mean (SD)	18.1 (18.33)	21.6 (17.95)
		Median	10.6	19.6
		IQR (Q3-Q1)	25.9	30.9
		Min, max	0, 62	0, 56
	All related SAEs	No. of patients	5	4
		Mean (SD)	2.3 (2.43)	16.8 (26.22)
		Median	1.0	5.6
		IQR (Q3-Q1)	3.1	29.9
		Min, max	0, 6	0, 56
Duration (days)	All TEAEs	No. of patients	1,417	1,420
		Mean (SD)	7.2 (11.66)	5.8 (9.97)
		Median	3.0	3.0
		IQR (Q3-Q1)	7.0	5.0
		Min, max	1, 129	1, 160
	All related TEAEs	No. of patients	396	557
		Mean (SD)	5.5 (9.90)	4.3 (6.40)
		Median	2.0	2.0
		IQR (Q3-Q1)	5.0	4.0
		Min, max	1, 94	1, 59
	All SAEs	No. of patients	64	66
		Mean (SD)	16.2 (23.85)	9.9 (15.44)
		Median	7.0	4.0
		IQR (Q3-Q1)	14.0	6.0
		Min, max	1, 129	1, 82
	All related SAEs	No. of patients	5	3
		Mean (SD)	14.8 (24.86)	3.3 (2.52)
		Median	6.0	3.0
		IQR (Q3-Q1)	6.0	5.0
		Min, max	1, 59	1, 6

[a]min, minimum; max, maximum; AE, adverse event; TEAE, treatment-emergent adverse event; SAE, serious adverse event; IQR, interquartile range; Q1, first quartile; Q3, third quartile.

mild or moderate, with 1 severe event (0.1%) in the oritavancin group and 2 severe events (0.2%) in the vancomycin group. No patient receiving oritavancin experienced an AE of red man syndrome, whereas 2 patients (0.2%) treated with vancomycin experienced an AE of red man syndrome. Fewer oritavancin-treated patients ($n = 6$; 0.6%) than vancomycin-treated patients ($n = 14$; 1.4%) discontinued study drug due to hypersensitivity AEs. Serious events of hypersensitivity occurred in 0.4% of patients in both treatment groups. The mean (standard deviation [SD]), median, and interquartile range (IQR) of the times to onset of hypersensitivity were 2.82 (4.613), 1.2, and 3.4 days, respectively, in the oritavancin group (range, 0 to 29 days) and 2.33 (4.156), 0.4, and 2.15 days, respectively, in the vancomycin group (range, 0 to 21 days). This difference was driven by substantially fewer oritavancin-treated patients ($n = 22$; 2.3%) than vancomycin-treated patients ($n = 68$; 6.9%) experiencing hypersensitivity AEs (mostly histamine-like infusion reactions [HLIRs]) within 6 h after initiation of the study treatment. Similarly, fewer oritavancin-treated patients ($n = 5$; 0.5%) than vancomycin-treated patients ($n = 17$; 1.7%) experienced hypersensitivity AEs with an onset of

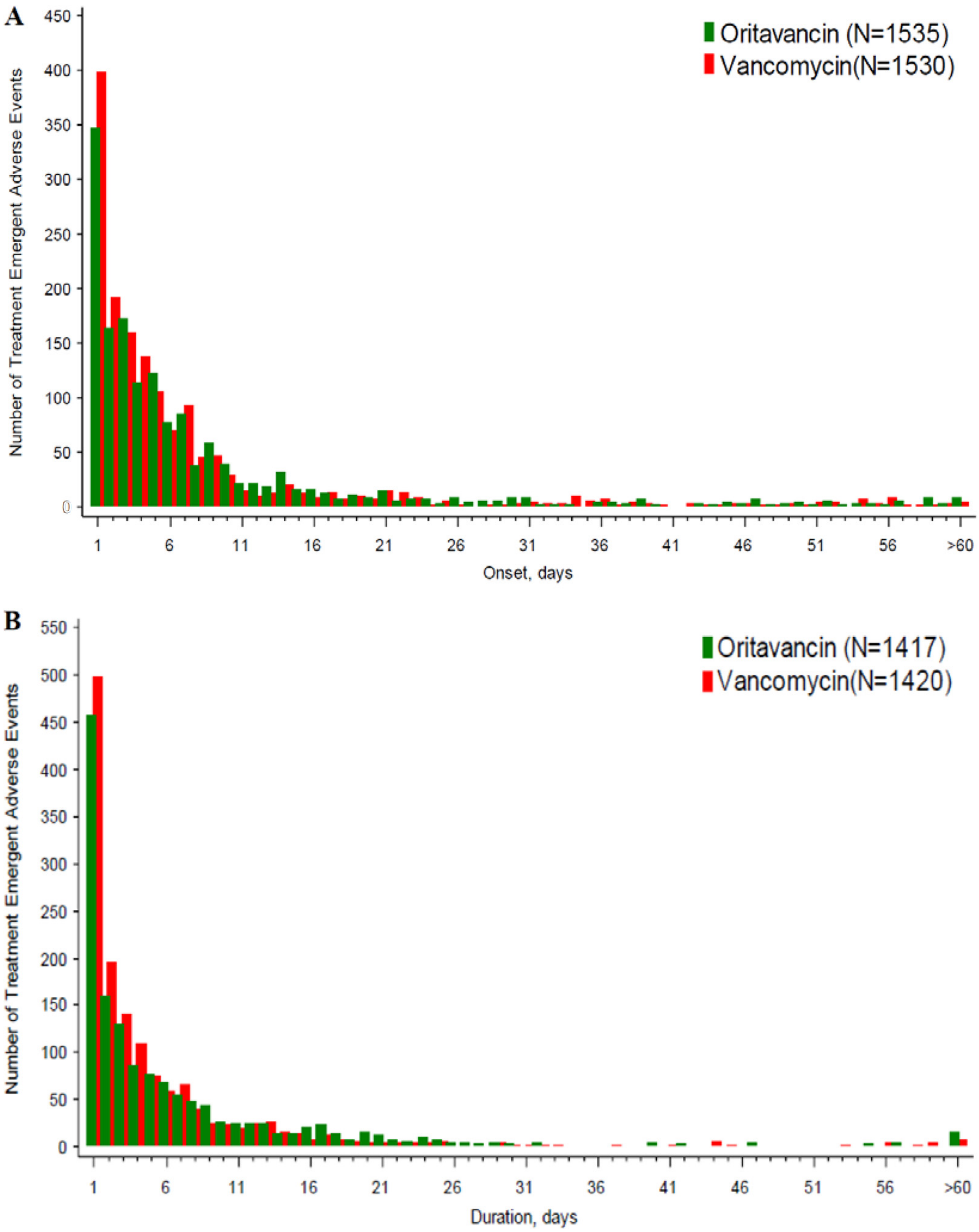

FIG 1 Distribution of time to onset (A) and duration (B) of treatment-emergent adverse events in patients with *Staphylococcus aureus* infection.

greater than 7 days. The mean (SD), median, and IQR of the durations of hypersensitivity were 5.09 (7.679), 2.4, and 5.14 days, respectively, in the oritavancin group (range, 0 to 45 days) and 4.06 (7.513), 1.0, and 5.27 days, respectively, in the vancomycin group (range, 0 to 52 days). No hypersensitivity events led to death in either group.

The incidence of infusion site reactions and/or phlebitis was 7.4% in the oritavancin group and 9.2% in the vancomycin group. The median time to onset of infusion site reactions/phlebitis was similar in both groups (oritavancin group, 3.2 days; vancomycin group, 3.1 days). Eighty percent of the infusion site reaction/phlebitis AEs in patients receiving oritavancin occurred after day 1, the day on which active study drug was infused. It is important to note that in order to maintain the blind in the SOLO studies, patients treated with oritavancin continued to receive infusions of placebo after the first dose of active drug. No oritavancin-treated patient and 2 (0.2%) vancomycin-treated patients experienced serious infusion site reactions/phlebitis. The proportion of patients who discontinued study drug because of infusion site reaction/phlebitis was 0.4% for the oritavancin group and 0.1% for the vancomycin group.

The incidence of vestibular toxicity was similar in the oritavancin (3.0%) and vancomycin (2.8%) groups, and none of the events were serious or led to discontinuation or death. The majority of vestibular toxicity AEs occurred in the first 14 days for each treatment group (oritavancin group, 28/29 patients; vancomycin group, 26/28 patients), with the remainder occurring between 14 and 30 days after initiation of study drug. The percentage of patients with AEs in the system organ class (SOC) of ear and labyrinth disorders was also similar in the oritavancin and vancomycin groups.

Infection-related adverse events. The percentage of patients in the SOLO pool with AEs in the SOC of infections and infestations was similar in the oritavancin (16.4%) and vancomycin (14.4%) groups. Whereas most infection and infestation AEs were mild or moderate, the number of patients with severe infection and infestation AEs was low and similar in both groups (oritavancin group, 21 [2.2%] patients; vancomycin group, 20 [2.0%] patients). Together, AEs of abscess limb and subcutaneous abscess were reported in 3.8% of patients in the oritavancin group and 2.3% of patients in the vancomycin group. The majority of these AEs corresponded to new infections, as opposed to worsening of the index infection, in both treatment groups. The median time to onset of a treatment-emergent abscess was shorter in the oritavancin group (12.8 days; range, 0 to 60 days) than in the vancomycin group (18.7 days; range, 0 to 57 days). Abscess limb, subcutaneous abscess, and skin bacterial infection together led to study drug discontinuation for 4 oritavancin-treated patients and 3 vancomycin-treated patients (Table 4).

In the database of pooled safety data from the SOLO studies, more patients in the oritavancin group (6 patients; 0.6%) than in the vancomycin group (1 patient; 0.1%) were reported to have an AE of osteomyelitis. The median time to osteomyelitis onset was 4.6 days (range, 0 to 9 days) for the patients in the oritavancin group and 2.6 days for the patient in the vancomycin group. In the oritavancin group, osteomyelitis was reported to have occurred on day 1 (2 patients), day 3 (1 patient), day 7 (2 patients), or day 9 (1 patient). The median duration of osteomyelitis was 26.8 days in the oritavancin group (range, 6 to 35 days) and 81 days in the single patient with osteomyelitis in the vancomycin group. The osteomyelitis event was categorized as serious for 4 patients (0.4% of the total pool) in the oritavancin group and 1 patient (0.1%) in the vancomycin group (Table 3). The investigator deemed osteomyelitis to be preexisting in 2 of these 4 oritavancin-treated patients, and another of these 4 patients had an inserted plate (right tibia) in close proximity to the primary infection (below the knee to below the malleoli). The osteomyelitis AE led to study drug discontinuation for 3 oritavancin-treated patients and 1 vancomycin-treated patient (Table 4). No osteomyelitis events in either group resulted in death.

Antibiotic-related effects, including *Clostridium difficile*-associated diarrhea (CDAD) and superinfection due to overgrowth by bacteria or fungi, have been reported with nearly all antibacterial agents. In the SOLO studies, no deaths, SAEs, or study drug discontinuations due to pseudomembranous colitis or CDAD were reported in either treatment group. One event of moderate clostridial infection that was determined to be possibly related to study drug and that lasted 3 days was reported in the oritavancin group. No AEs of pseudomembranous colitis or CDAD were reported in the vancomycin group. No patient in the SOLO pool had a bacterial or fungal superinfection.

Renal and hepatic adverse events. The incidence of renal AEs was low and similar in the two groups, occurring in 7 (0.7%) oritavancin-treated patients and 9 (0.9%) vancomycin-treated patients. In total, renal failure was reported for 3 (0.3%) patients in the oritavancin group and 5 (0.5%) patients in the vancomycin group; one event in the vancomycin group was reported to be serious. No renal failure events were reported to be severe, and no deaths or discontinuations of study drug due to a renal AE occurred.

There were no changes in urinalysis parameters suggestive of a nephrotoxic effect of oritavancin. For serum blood urea nitrogen and creatinine, the percentage of patients with a potentially clinically significant (PCS) change was also similar in the oritavancin and vancomycin groups. There were 13/916 (1.4%) oritavancin-treated patients and 19/920 (2.1%) vancomycin-treated patients with PCS increases in the serum creatinine concentration (i.e., increases to ≥2 mg/dl postbaseline). For the 9 oritavancin-treated patients and 10 vancomycin-treated patients for whom the time to resolution of the increase in the serum creatinine concentration (i.e., to a result below 2 mg/dl prior to the end of the study) could be assessed, the mean (SD), median, and IQR of the times to resolution were 12.1 (6.06), 13.7, and 10.1 days, respectively, for oritavancin-treated patients and 15.5 (8.99), 14.1, and 4.2 days, respectively, for vancomycin-treated patients. Similarly, changes in creatinine clearance levels were similar between the oritavancin and vancomycin groups and were not clinically significant.

A comprehensive evaluation of liver safety was performed on the safety population by examining liver function test (LFT) findings from laboratory analyses and AEs related to liver laboratory test abnormalities or clinical AEs. The percentage of patients with hepatic clinical AEs was 4.7% in the oritavancin group and 3.0% in the vancomycin group. This difference was partially driven by the preferred term of alanine aminotransferase (ALT) increase, which was reported as an AE in 2.8% (oritavancin group) and 1.5% (vancomycin group) of patients. The majority of these events were mild or moderate; however, there were 2 events of severe increases in ALT levels in the vancomycin group (0.2%) and none in the oritavancin group. There were no SAEs related to hepatic effects or hepatic AEs leading to study drug discontinuation or death in either group. Liver enzyme elevations in both groups were transient and asymptomatic, mean changes from the baseline for each liver function test parameter were similar in both the oritavancin and vancomycin groups, none of these changes were clinically significant, and none of the patients discontinued study drug due to liver enzyme elevations. Medical review of all the individual cases and evaluation of drug-induced serious hepatotoxicity (eDISH) confirmed that none of these events met established criteria for drug-induced liver injury (i.e., Hy's law [34]). Of the 24 patients (10 in the oritavancin group, 14 in the vancomycin group) in the safety population with aspartate aminotransferase (AST) or ALT elevations >5 times the upper limit of the normal range (ULN), AST and ALT values returned to baseline levels for 17 patients (8 in the oritavancin group, 9 in the vancomycin group). Mean (SD), median, and IQR of the times to resolution for patients with increases in ALT or AST to at least 5 times the ULN were 14.42 (22.52), 6.92, and 6.06 days, respectively, for the oritavancin group and 7.91 (2.982), 7.96, and 5.02 days, respectively, for the vancomycin group. For the remaining 7 patients, either AST or ALT values decreased as of the last available assessment or the patients were lost to follow-up. On the basis of a rigorous evaluation of liver-related events within the safety population, oritavancin did not cause drug-induced liver injury.

Special populations and subgroup analyses of safety. For both treatment groups, SAEs and discontinuations of study drug due to an AE were more frequent in patients ≥65 years old than patients <65 years old. Similarly, patients who weighed ≥100 kg or who had a BMI of ≥30 kg/m² had higher rates of AEs, SAEs, and AEs leading to study drug discontinuation in both treatment groups than did patients with a BMI of <30 kg/m² and patients who weighed <100 kg (Table S2). These higher rates were not due to differences in the rates of any specific AEs at the preferred term level. The incidence of SAEs and of AEs leading to study drug discontinuation was slightly higher in diabetics treated with oritavancin than diabetics treated with vancomycin; this was primarily due to events in the infections and infestations SOC. Diabetic patients also had higher rates of AEs, SAEs, and AEs leading to study drug discontinuation than nondiabetic patients. In patients with moderately impaired renal function (CL_{CR}, 30 to <60 ml/min), 12/70 (17.1%) in the oritavancin group experienced an SAE, whereas 3/54 (5.6%) subjects in the vancomycin arm experienced an SAE. In patients with severely impaired renal function (CL_{CR}, <30 ml/min), 0/7 in the oritavancin group and 1/7

(14.3%) in the vancomycin group experienced an SAE, and the event in the patient in the vancomycin group led to discontinuation. The incidence of AEs, SAEs, and AEs leading to study drug discontinuation for patients with hepatic impairment was somewhat higher in the oritavancin group than in the vancomycin group; however, there were few hepatically impaired patients in the safety population overall (oritavancin group, 29 [3.0%] patients; vancomycin group, 27 [2.7%] patients).

Clinical laboratory evaluations. For each hematology and chemistry parameter, the incidence of shifts from normal at the baseline to either high or low after the baseline were similar in the oritavancin and vancomycin groups in the pooled data from the SOLO studies. The percentage of patients with potentially clinically significant values in each hematology and chemistry parameter at any time postbaseline was also similar in the oritavancin and vancomycin groups. Mean changes from the baseline for each LFT parameter were similar in both the oritavancin and vancomycin groups in each pool, and none of these changes were clinically significant.

DISCUSSION

In this safety analysis of pooled data from the SOLO studies, over 900 subjects were included in both treatment groups. Overall, a single 1,200-mg dose of oritavancin had a safety profile similar to that of vancomycin, which was administered twice daily for 7 to 10 days in SOLO I and SOLO II (28, 29). The frequency, distribution, and severity of AEs that emerged during treatment for ABSSSI were similar in the oritavancin and vancomycin groups. Discontinuations of study treatment due to AEs were uncommon. No patterns of SAEs could be discerned in either treatment group, and the vast majority of events were considered by the investigator to be unrelated to study drug. In addition, no clinically significant between-group differences in clinical laboratory values were observed. The incidence and types of AEs were comparable for oritavancin- and vancomycin-treated patients within each analyzed subgroup; however, the incidence of SAEs and AEs leading to discontinuations of study drug generally increased with an increase in the extent/severity of each comorbid condition, as may also be seen in general clinical practice.

The prolonged plasma elimination half-life of oritavancin (27) could raise concerns about late-onset or extended-duration AEs should an adverse reaction to this antibiotic occur. A 60-day safety follow-up visit was included in the SOLO studies to assess the patients for any late-onset toxicities. In this pooled analysis, the onset and duration of AEs were similar for the oritavancin and vancomycin groups, and late-onset events were infrequent and were observed at a similar rate in the two treatment groups.

Osteomyelitis was reported in a small number of subjects, and it occurred more frequently in subjects receiving oritavancin. The SOLO study protocols did not allow for enrollment of patients with suspected or documented osteomyelitis. In a review of all these cases, osteomyelitis AEs in patients treated with oritavancin occurred soon after study enrollment, indicating that the osteomyelitis was likely present at the baseline but was unrecognized. Furthermore, all cases of osteomyelitis in oritavancin- and vancomycin-treated patients were considered unrelated to study drug by the investigator.

The results of a pharmacokinetic subgroup analysis of the SOLO studies confirmed that the recommended clinical dose of oritavancin (1,200 mg administered over 3 h as an i.v. infusion) is appropriate regardless of differences in patient age, body size, gender, race, mild to moderate renal impairment, or presence of diabetes, with no dosage adjustment being required for any of these subgroups (27). These results are consistent with the observed efficacy in these special patient populations within the individual SOLO studies (28, 29, 31) and are supported by the pooled safety data from the SOLO studies presented here.

In conclusion, a single 1,200-mg dose of oritavancin was well tolerated and had a safety profile similar to that of 7 to 10 days of twice-daily vancomycin treatment in adults with ABSSSI caused by Gram-positive bacteria. More than 80% of the AEs in the phase 3 SOLO studies were mild to moderate in severity. The incidences of death, SAEs, and discontinuation of study drug due to an AE in oritavancin-treated patients were low and similar to those in patients receiving vancomycin. No unforeseen events were attributable to oritavancin's long terminal plasma half-life, and the AEs observed with oritavancin were not prolonged in time to onset or duration compared to those observed with vancomycin. The SOLO studies demonstrated that oritavancin is a safe, single-dose alternative to multiday, twice-daily vancomycin for a variety of ABSSSI patient populations.

MATERIALS AND METHODS

Study design. SOLO I (28) and SOLO II (29) were randomized, double-blind studies of identical design comparing the efficacy and safety of a single 1,200-mg i.v. dose of oritavancin with i.v. dosing of vancomycin (1 g or 15 mg/kg of body weight every 12 h) for 7 to 10 days in adults with ABSSSI. An extended safety follow-up period of 60 days was incorporated, given the long plasma elimination half-life of oritavancin (27). The protocol for each study (28, 29) was approved by institutional review boards/ethics committees and was consistent with regulatory guidance to industry (35). All patients provided written informed consent.

Patient selection. Eligible patients had to be at least 18 years old and to have a diagnosis of ABSSSI that was suspected or proven to be due to a Gram-positive pathogen and that, in the judgment of the investigator, would require at least 7 days of i.v. therapy (28, 29). ABSSSI were defined as wound infections (either traumatic or surgical in origin), cellulitis/erysipelas, or major cutaneous abscess. Each lesion required surrounding erythema, edema, and/or induration of at least 75 cm^2. With some exceptions related to an age of >70 years, diabetes, or immunocompromise, patients also had to present with signs and symptoms of systemic inflammation.

Safety analyses. Safety analyses for the present study were based on pooled data from across both SOLO studies. Pooling was appropriate because the protocols were identical in patient selection criteria, design, conduct, monitoring, and planned analyses and pooled analyses provided a larger patient sample with which to improve the precision in the estimate of any safety-related between-treatment differences in each patient subgroup.

Safety analyses were performed on all patients who were enrolled in SOLO I or II and received any study medication (the safety population) and included the occurrence of AEs, SAEs, discontinuations of study drug due to AEs, electrocardiograms (ECG), and changes in safety laboratory parameters. All AEs, regardless of treatment group or suspected causal relationship to study drug, were reported for each patient for the period between consent and study day 60 or, for patients with ongoing AEs at day 60, until the AE had resolved or the patient was lost to follow-up. The relatedness of each AE to study drug was assessed by the investigator, who was unaware of the treatment assignment, to be unrelated (clearly due to causes other than study drug), unlikely to be related (no reasonable evidence or argument to suggest a causal relationship between study drug and the AE), possibly related (reasonable evidence or an argument to suggest a causal relationship between the AE and study drug), or definitely related (related to study drug with a high degree of certainty).

Subgroup analyses of safety were performed by patient age (<65 and ≥65 years), body weight (<60, 60 to <100, and ≥100 kg), body mass index (BMI; <25, 25 to <30, and ≥30 kg/m^2), renal function (Cockcroft-Gault equation-estimated creatinine clearance [CL_{CR}] of <30, 30 to <60, 60 to <90, and ≥90 ml/min), diabetic status, and hepatic impairment (baseline alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level >3 times the upper limit of the normal range [ULN] or total bilirubin level >2 times the ULN). Standard hematology and chemistry safety laboratory tests were performed at each visit.

Continuous variables were summarized by treatment group using descriptive statistics, including the number of patients (*n*), mean, standard deviation (SD), median, minimum (min), and maximum (max). Categorical variables were summarized by treatment group using frequency and percentage. AEs were summarized regardless of relationship to study drug. AEs were coded by MedDRA (version 13.1) and summarized by frequency, severity, relationship to study drug as assessed by the investigator, onset, and duration using the primary system organ class (SOC) and preferred term.

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/AAC.01919-17.

SUPPLEMENTAL FILE 1, PDF file, 0.2 MB.

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